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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,571	12/05/2003	Marie Anderson	ASZD-P01-007	8775

44992 7590 04/18/2006

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 04/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/729,571	ANDERSON ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,6,8-11 and 28-40* is/are pending in the application.

4a) Of the above claim(s) *28-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6 and 8-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/20/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-2, 5-6, 8-11, and 28-40 are pending in the application.

[2] Applicant's amendment to the claims, filed on 1/27/2006, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

Election/Restriction

[3] Initially, it is noted that applicant states "[r]estriction is required under 35 U.S.C. 121 and 372" at p. 7, top of the instant response. However, the instant application is not a filing under 35 U.S.C. 371 and the 12/29/2005 restriction requirement is not made under 35 U.S.C. 372. As such, unity of invention does not apply here.

[4] Applicant's election with traverse of Group I, claims 1, 5-6, and 8-11, in the response filed on 1/27/2006, is acknowledged. The traversal is on the ground(s) that Groups I and VI have the same class/subclass and searching the inventions of Groups I and VI would not place an undue burden on the examiner.

Although applicant's argument regarding the inventions of Groups I and VI having the same class/subclass is not found persuasive, it is noted that a search for Groups I and VI would not appear to place an undue burden on the examiner. The specification discloses that a crystal of *H. pylori* MurI complexed with the substrate glutamate and the inhibitor of compound A has the same space group and unit cell dimensions of a crystal of *H. pylori* MurI complexed with only

inhibitor compound A (see descriptions of Figures 6 and 7 at p. 5 of the specification and line 16 of Figure 6A and line 16 of Figure 7A of the drawing figures). The presence of the substrate does not appear to alter the structure of the crystal of the co-compelx of *H. pylori* MurI/compound A. Thus, it would not appear to place an undue search burden on the examiner and upon reconsideration of the restriction requirement, the examiner has rejoined claim 2 with claims 1, 5-6, and 8-11 of elected Group I for examination on the merits.

With regards to remaining claims 28-40, applicant does not traverse the restriction requirement. Thus, for these claims the requirement is still deemed proper and is therefore made FINAL.

[5] Claims 28-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **with** traverse in the reply filed on 1/27/2006.

Priority

[6] Applicant's claim for domestic priority under 35 USC § 119(e) to US provisional applications 60/435,167, 60/435,272, 60/435,087, and 60/435,527, all filed on 12/20/2002, is acknowledged. See the application data sheet filed on 12/5/2003.

Specification

[7] It is noted that the specification states, "[t]he present application is related to" the following US provisional applications: 60/435,167, 60/435,272, 60/435,087, and 60/435,527 (specification at p. 1, lines 8-14). The specification is objected to and should be amended to specifically state that the present application claims domestic priority under 35 USC § 119(e) to the provisional applications.

Sequence Compliance

[8] This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or

1.825(d). See particularly sequences disclosed at pp. 133-135 and 137 of the specification.

Information Disclosure Statement

[9] All references cited in the information disclosure statement filed on 10/20/2004 have been considered by the examiner. A copy of Form PTO/SB/08 is attached to the instant Office action.

Claim Objections

[10] Claims 1-2, 5-6, and 8-11 are objected to in the recitation of "*H. pylori*" and "Murl." Abbreviations should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[11] Claim(s) 1-2, 5-6, and 8-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 1-2, 5-6, and 8-11 are indefinite in the recitation of "*H. pylori* Murl" as neither the specification nor the claims teaches the identifying characteristics

that distinguishes an "*H. pylori* MurI" polypeptide from other glutamate racemase enzymes. While the application teaches many physical properties of an "*H. pylori* MurI" polypeptide (see, *e.g.*, p. 21, lines 1-16), it fails to define which characteristics or properties are necessary to be encompassed by the scope of recited "*H. pylori* MurI" polypeptides. It is suggested that applicant clarify the meaning of the claims.

[b] Claim 6 is indefinite in the recitation of "a substrate binding site," "an activator binding site," "an intermolecular dimer interface," "an intradomain interface," and "an inhibitor binding site" as it is unclear as to the amino acid(s) of an *H. pylori* MurI that are intended as being encompassed by the terms "a substrate binding site," "an activator binding site," "an intermolecular dimer interface," "an intradomain interface," and "an inhibitor binding site." Consequently, it is unclear as to the scope of claimed crystals. It is suggested that applicant clarify the meaning of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[12] Claim(s) 1-2, 5-6, and 8-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to a genus of crystals of *H. pylori* MurI complexed with inhibitor or complexed with inhibitor and substrate, optionally wherein the inhibitor is bound to a MurI molecular interface. In order to clarify the record, it is noted that the term "molecular interface" has been interpreted as meaning any portion or part of an *H. pylori* MurI polypeptide.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.,* structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 further states that a "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification fails to disclose even a single representative species of the genus of claimed crystals. While it is noted that the specification discloses representative species of crystals of an *H. pylori* MurI produced and purified according to the method set forth at pp. 90-95 of the specification having the space group and unit cell dimensions as

set forth at p. 100, lines 20-22; p. 101, lines 9-11, 19-21, and 30-32, and p. 102, lines 8-10. Other than these representative species, the specification fails to disclose any other crystals of *H. pylori* MurI, which encompasses widely variant species, including crystals of *any* polypeptide considered to be an *H. pylori* MurI polypeptide complexed with *any* inhibitor bound to *any* molecular interface and optionally *any* substrate, wherein the crystal has *any* space group and *any* unit cell dimensions. It is noted that a number of variants of *H. pylori* MurI are known in the art. See Appendix A which shows an alignment of SEQ ID NO:2 with a known variant of *H. pylori* MurI.

Further, it is noted that the genus of claimed crystals is limited to those of an "*H. pylori* MurI" (emphasis added). In this case, the specification fails to convey the common structural characteristics of an "*H. pylori* MurI" such that one can visualize the members encompassed by the genus and distinguish a subgenus of "*H. pylori*" MurI polypeptides from the broader genus of MurI polypeptides from any source.

Given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[13] Claims 1-2, 5-6, and 8-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for crystals of an *H. pylori* MurI produced and purified according to the method set forth at pp. 90-95

of the specification having the space group and unit cell dimensions as set forth at p. 100, lines 20-22; p. 101, lines 9-11, 19-21, and 30-32, and p. 102, lines 8-10, does not reasonably provide enablement for all *H. pylori* MurI crystals as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: The claims are so broad as to encompass crystals of *any* polypeptide considered to be an *H. pylori* MurI polypeptide complexed with *any* inhibitor bound (including any small molecule inhibitor, any neutralizing antibody, etc.; it should be noted that the "inhibitor" need not be an *H. pylori* MurI inhibitor) to *any* molecular interface and optionally *any* substrate (it should be noted that the "substrate" need not be a *H. pylori* MurI substrate), wherein the

crystal has *any* space group and *any* unit cell dimensions. The broad scope of claimed crystals and crystallization methods is not commensurate with the enablement provided by the disclosure. In this case the disclosure is limited to crystals of an *H. pylori* MurI produced and purified according to the method set forth at pp. 90-95 of the specification having the space group and unit cell dimensions as set forth at p. 100, lines 20-22; p. 101, lines 9-11, 19-21, and 30-32, and p. 102, lines 8-10.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The state of the art at the time of the invention acknowledges a high level of unpredictability for making a diffraction-quality protein crystal. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "[w]ell-ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1995) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (*Biophys Chem* 91:1-20), which teaches

that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). Also, the reference of Buts *et al.* (*Acta Crystallogr. D.* 61:1149-1159) teaches that "[f]ive naturally occurring variants, differing in 1-18 amino acids, of the 177-residue lectin domain of the F17G fimbrial adhesin were expressed and purified in identical ways. For four out of the five variants crystals were obtained, mostly in non-isomorphous space groups, with diffraction limits ranging between 2.4 and 1.1 Å resolution" and that crystallization of protein variants that differed from a parent sequence by only a single amino acid resulted in different crystal forms with distinct diffraction properties (see Tables 1-3). Thus, in view of these teachings, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of other *H. pylori* MurI polypeptides complexed with any inhibitor and optionally substrate, wherein the inhibitor is bound to any part of the *H. pylori* MurI polypeptide as encompassed by the claims can be achieved using the disclosed crystallization conditions.

The amount of direction provided by the inventor; The existence of working examples: Branden et al. acknowledges that solving the three-dimensional structure of a protein requires a diffraction-quality crystal (p. 374). In this case, while the specification discloses working examples of diffraction-quality *H. pylori* MurI crystals, the specification fails to provide the necessary guidance for

crystallizing any other "*H. pylori* MurI" polypeptides complexed with *any* inhibitor and optionally *any* substrate to generate a diffraction-quality crystal.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallography were known at the time of the invention, it was not routine in the art to screen for all crystals of an "*H. pylori* MurI" polypeptide complexed with *any* inhibitor and optionally *any* substrate to generate a diffraction-quality crystal.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use all crystals and polypeptides as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Citation of Relevant Art

[14] The art made of record and not relied upon is considered pertinent to applicant's disclosure. Lee et al. (*Acta Cryst* F61:199-201) discloses a crystal of *Lactobacillus fermenti* glutamate racemase and Taal et al. (*Acta Cryst* D60:2031-2034) discloses a crystal of *Bacillus subtilis* glutamate racemase.

Conclusion

[15] Status of the claims:

- Claims 1-2, 5-6, 8-11, and 28-40 are pending.
- Claims 28-40 are withdrawn from further consideration.
- Claims 1-2, 5-6, and 8-11 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656

APPENDIX A

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Q6VRG6_HELPY
ID   Q6VRG6_HELPY PRELIMINARY;      PRT;   255 AA.
AC   Q6VRG6;
DT   05-JUL-2004 (TrEMBLrel. 27, Created)
DT   05-JUL-2004 (TrEMBLrel. 27, Last sequence update)
DT   05-JUL-2004 (TrEMBLrel. 27, Last annotation update)
DE   Glutamate racemase.
GN   Name=glr; ORFNames=HP0549;
OS   Helicobacter pylori (Campylobacter pylori).
OC   Bacteria; Proteobacteria; Epsilonproteobacteria; Campylobacterales;
OC   Helicobacteraceae; Helicobacter.
OX   NCBI_TaxID=210;
RN   [1]
RP   NUCLEOTIDE SEQUENCE.
RC   STRAIN=Du23:2;
RX   PubMed=15019987; DOI=10.1016/j.gene.2003.11.029;
RA   Blomstergren A., Lundin A., Nilsson C., Engstrand L., Lundeberg J.;
RT   "Comparative analysis of the complete cag pathogenicity island
RT   sequence in four Helicobacter pylori isolates.";
RL   Gene 328:85-93(2004).
DR   EMBL; AY330644; AAR03971.1; -; Genomic_DNA.
DR   HSSP; P56868; 1B74.
DR   GO; GO:0005618; C:cell wall; IEA.
DR   GO; GO:0008881; F:glutamate racemase activity; IEA.
DR   GO; GO:0016853; F:isomerase activity; IEA.
DR   GO; GO:0000902; P:cellular morphogenesis; IEA.
DR   GO; GO:0008152; P:metabolism; IEA.
DR   GO; GO:0009252; P:peptidoglycan biosynthesis; IEA.
DR   InterPro; IPR001920; Asp/Glu_race.
DR   InterPro; IPR004391; Glu_race.
DR   Pfam; PF01177; Asp_Glu_race; 1.
DR   TIGRFAMs; TIGR00067; glut_race; 1.
DR   PROSITE; PS00923; ASP_GLU_RACEMASE_1; 1.
DR   PROSITE; PS00924; ASP_GLU_RACEMASE_2; 1.
SQ   SEQUENCE   255 AA;  28321 MW;  FFB32C880EE92C07 CRC64;

  Query Match             95.0%;  Score 1249;  DB 2;  Length 255;
  Best Local Similarity   94.5%;  Pred. No. 1.8e-96;
  Matches  241;  Conservative    8;  Mismatches    6;  Indels    0;  Gaps    0;

Qy          1 MKIGVFDSGVGGFSVLKSLLKARLFDEIIYYGDSARVPYGTKDPTTIKQFGLEALDFFKP 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Qy         61 HEIELLIVACNTASALALEEMQKYSKIPIVGVIEPSILAIKRQVEDKNAPILVLGTKATI 120
              |:| ||||||||||||||||||:||||||||||||||:||:|||||||||||||||
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Qy        121 QSNAYDNALKQQGYLNISHLATSLFVPLIEESILEGELLETCMHYYFTPLEILPEVIILG 180
              ||||||||||||||||:|||||||||||||||||||||||| ||||||:|||||||||
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Qy        241 DVIWLERQAKEWLKL 255
              ||:|||:||||||||
Db        241 DVVWLEKQAKEWLKL 255
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